

Remarks

I. Status of the Claims

Claims 3, 6, 7, 21, 24, 25, 39, 42, 43, 57, 60, 61, 81, 84, and 85 have been amended, no claims have been canceled, and no claims have been added in the amendments submitted herewith. Claims 1-96 are therefore presently pending and claims 1-8 and 68-73 are under consideration in the application.

II. Amendments to the Claims

Claims 3, 6, 7, 21, 24, 25, 39, 42, 43, 57, 60, 61, 81, 84, and 85 have been amended to delete the phrase "or inhibiting". Applicants explicitly reserve the right to file one or more continuing applications to the deleted subject matter.

III. Elected and Examined Subject

The Office Action dated October 16, 2008 in the third paragraph, page 2 states "claim 1 is partially directed to a species that is independent...". Is it the Examiner's view that only part of claim 1 is pending and has been searched, namely the part to the extent it reads upon formula III?

The Examiner is respectfully reminded of the procedure to be followed in election of species practice as stated in the MPEP §803.02 6th paragraph, "[s]hould applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The examination **will be extended** (emphasis added) to the extent necessary to determine patentability of the Markush-type claim." Applicants believe the present amendments overcome the enablement rejection made by the Examiner and believe the arguments below overcome the obviousness rejection made by the Examiner. Thus, Applicants' request that examination be extended to encompass the remaining claimed compounds of formulas I, II, IV, and IV.

III. Rejections of claims under 35 U.S.C. § 112, First Paragraph

The Office Action, dated October 16, 2008 rejects claims 3-8 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement concerning the phrase, "or inhibiting". The Examiner states the phrase "is analogous to 'prevention'". The present amendments, removing the phrase overcomes this rejection.

IV. Rejections of claims under 35 U.S.C. § 103(a)

Claims 1-8 and 68-73 have been rejected as obvious over Creemer ('906) in view of Gutman (Toxins and Signal Transduction) and Zhu ('547). The Examiner states Gutman (Toxins and Signal Transduction) teaches the limited solubility and instability in water of wortmannin. Wortmannin as such, water solubility, and water stability are not limitations of the present claims. To the contrary, Applicants' compounds differ in structure from wortmannin, are soluble in water, and are stable in water. Gutman (Toxins and Signal Transduction) does not supply any part of the present claim. Applicants assume that the rejection was intended to be over Creemer ('906) in view of Zhu ('547) with motivation supplied by Gutman (Toxins and Signal Transduction). Applicants also assume the teaching of Zhu ('547) was intended to be -O-(CO)-(CH₂)-S-(CH₂CH₂)-PEG- (emphasis added), otherwise the teaching would not fit Applicants' claims.

Applicants make five arguments concerning this rejection. Firstly, the MPEP in §2143.02 requires a reasonable expectation of success in making the change to the prior art urged by the Examiner. The MPEP states in Section II, "AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS"

"Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)."

Applicants submit as evidence GREENWALD (J. Controlled Release), which states in then first sentence of the abstract, “[n]o low molecular weight (<20 000) poly(ethylene glycol) (PEG) small molecule drug conjugates, prepared over a 20-year period, have led to a clinically approved product.” Applicants’ formula III is a small molecule drug conjugated to a 5000 molecular weight modified PEG. The molecular weight of Applicants working example of formula III is found in lines 3-18, page 30. One reason for GREENWALD (J. Controlled Release) to make the conclusion above is found in the paragraphs 2 and 3.1 spanning pages 160 to 161. Conjugation of small molecule drugs with <20 000 PEG chains is art recognized to dramatically lower the *in vitro* activity and show no activity *in vivo*. By contrast to the predictions of GREENWALD (J. Controlled Release), Applicants’ conjugated compounds show better activity in the *in vitro* Thymidine and MTS assays than does the unconjugated drug. This is found on page 38 of the specification. Compound III without the water-soluble portion is 17-dihydrowortmannin. Even more striking are the *in vivo* results in the U87MG mouse xenograph model found on page 36. Applicants’ conjugated compound III shows a lower tumor volume (44%) than does control. Applicants’ conjugated compound III is even much better than the unconjugated drug (60% of control). GREENWALD (J. Controlled Release) in the last sentence paragraph 3.1, page 161 emphasizes, “the necessity for *in vivo* testing to verify *in vitro* cytotoxicity results”.

Secondly, the solubility of rapamycin, the compound modified by Zhu (‘547) is about 1 µg/ml. As evidenced by Holleran (Drug Metab Dispos) in the last paragraph, page 492, the solubility of wortmannin is 300 µM. This is far above the 5 nM IC₅₀ for PI3K inhibition, which is the mechanism of action of wortmannin. Using the molecular weight of 428.44 for wortmannin, one can easily calculate that the water solubility of wortmannin is about 130 µg/ml, *i.e.* 130 times greater than for rapamycin. Increasing the water solubility of wortmannin was not the motivation for preparing the conjugates of the present application. In fact, there is no need to increase the water solubility, since its solubility exceeds the IC₅₀ by a factor of 60,000.

Thirdly, the MPEP §2141.02 pertains to “[a]scertaining the differences between the prior art and the claims at issue”. Creemer (‘906) teaches the wortmannin core with “R₂ =

OR₃; each R₃ individually is hydrogen, arylacyl, C₃-C₈acyl or substituted acyl". Creemer ('906) does not teach the wortmannin core with R₂ = phenyl as stated by the Examiner. Applicants' formula III has a -O-(CO)-(CH₂)-S-(CH₂CH₂O)_n-CH₃ radical where n is 1-1000 attached to position 17 (the Creemer ('906) R₂ radical). The only working example in Creemer ('906) with R₂ = acyl is formula (j), column 11, which has an acetyl -O-(CO)-CH₃ radical as R₂. Compound (j) in Creemer ('906) also has a propionyl group at the C-11 position (radical R₁). Applicants' formula III requires an acetyl group at this position. This is a second difference between the species taught by Creemer ('906) and Applicants' formula III.

Zhu ('547) teaches a derivative of rapamycin called SDZ-RAD conjugated with the -O-(CO)-(CH₂)-S-(CH₂CH₂O)_n-CH₃ radical where n is 5-450 in lines 1-17, column 3. Rapamycin is a macrocyclic lactone with a twenty-nine membered central ring. Applicants' formula III has a furanosteroid with five fused six- and five-membered rings. Zhu ('547) teaches conjugation through a primary alcohol. Applicants' formula III is conjugated through a secondary alcohol. The rapamycin core taught by Zhu ('547) contains nitrogen. Applicants' formula III does not. This is not the usual ethyl *versus* methyl obviousness situation.

Fourthly, rapamycin, which forms the core of Zhu's ('547) teaching, according to Wikipedia, "bind[s] the cytosolic protein FK-binding protein 12 (FKBP12) in a manner similar to tacrolimus. However, unlike the tacrolimus-FKBP12 complex which inhibits calcineurin (PP2B), the [rapamycin]-FKBP12 complex inhibits the mammalian target of rapamycin (mTOR) pathway by directly binding the mTOR Complex1 (mTORC1). mTOR is also called FRAP (FKBP-rapamycin associated protein) or RAFT (rapamycin and FKBP target). The IC₅₀ for the inhibition of mTOR activity by rapamycin alone is 77,000 nM while The IC₅₀ for rapamycin + FKBP 12 is 56 nM."

By contrast wortmannin, used to make Applicants' formula III, is according to Wikipedia, "a specific, covalent inhibitor of phosphoinositide 3-kinases (PI3Ks). [Wortmannin] has an *in vitro* inhibitory concentration (IC₅₀) of around 5 nM, making it a more potent inhibitor than LY294002, another commonly used PI3K inhibitor.

[Wortmannin] displays a similar potency *in vitro* for the class I, II, and III PI3K members although it can also inhibit other PI3K-related enzymes such as mTOR, DNA-PK, some phosphatidylinositol 4-kinases, myosin light chain kinase (MLCK) and mitogen-activated protein kinase (MAPK) at high concentrations. Wortmannin has also been reported to inhibit members of the polo-like kinase family with IC_{50} in the same range as for PI3K.” Wortmannin has an *in vitro* inhibitory concentration (IC_{50}) of around 730 nM against mTOR, which is only 0.7% of its potency against PI3K. Wortmannin and rapamycin are simply different compounds with different mechanisms of action. Wortmannin is a biochemical tool, not used clinically. Rapamycin has demonstrated anticancer effects in humans.

Fifthly, the MPEP §2141 III. (E) states a conclusion of obviousness can be supported by a rationale of, “[o]bvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success”. In line 11, page 8 of the Office Action of October 16, 2008, the Examiner states “Zhu et al teaches the use of the of the conjugate ester –O-(CO)-(CH₂)-S-(CH₂)-PEG- as a means of increasing the solubility of otherwise insoluble compound (column 3 lines 18-32)”. In fact, Zhu (‘547) teaches conjugation of only two compounds, SDZ-RAD and rapamycin, not all water insoluble compounds and not all compounds with known *in vitro* anti-proliferation activity. The number of compounds, like wortmannin, which are reported in the literature to inhibit tumor cell growth *in vitro* probably numbers in the hundreds of thousands, possibly millions. Does the Examiner argue that attachment of the side-chain pictured at position 17 in Applicants’ formula III to any or all of these millions of compounds of diverse structure is obvious? Such a conclusion is not supported by the requirement that the number of solutions be finite and be predictable.

V. Period for Reply

The Final Rejection set a three-month period to comply, to and including January 16, 2009. This response is believed to be timely filed. Should any additional fees be deemed necessary, Commissioner is authorized to charge Deposit Account No. 01-1425.

VI. Conclusion.

Applicants believe that the pending claims are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner issue a timely Notice of Allowance. The Commissioner is hereby authorized to charge any fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account 01-1425. The Examiner is encouraged to contact the undersigned by telephone, if such an interview on any matter could advance the prosecution of the present application.

Respectfully submitted,

A handwritten signature in black ink, reading "Thomas C. McKenzie". The signature is written in a cursive, flowing style with a large initial 'T' and a long, sweeping underline.

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